PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cochlear implantation for tinnitus in adults with bilateral hearing loss: protocol of a randomized controlled trial
AUTHORS	Assouly, Kelly; Smit, Adriana; Stegeman, Inge; Rhebergen, Koen S.; van Dijk, Bas; Stokroos, Robert

VERSION 1 – REVIEW

REVIEWER	Peter R Dixon University of Toronto Department of Otolaryngology-Head & Neck Surgery Toronto, Canada
REVIEW RETURNED	02-Sep-2020

GENERAL COMMENTS	This protocol describes a single centre randomised controlled trial designed to address the question of whether cochlear implantation reduces tinnitus burden for adults with bilateral sensorineural hearing loss whose primary indication for implantation is tinnitus. Novelty is predicated on recruiting patients who would not otherwise have met hearing loss criteria for cochlear implantation in the institution. The most important flaw of the protocol is justification for the comparator group. Despite evidence to support existing interventions for tinnitus, including cognitive behavioural therapy (Fuller et al. 2020, Cochrane), authors select a comparison group with no intervention. This should be more clearly justified in the protocol. Additional suggestions for improvement are listed below, with associated SPIRIT reporting items listed where relevant. Additional suggestions: • Title o The title would benefit from revision to more clearly indicate the population under study. For example, authors might consider some variation of: “Cochlear implantation for tinnitus in adults with bilateral hearing loss: A randomized controlled trial” • Introduction o The choice of comparator (item 6B) should be more clearly justified. Authors indicate that CBT is supported as a therapy for reducing tinnitus burden but choose a comparator group of no intervention. Why is CBT not compared? o Description of trial design (item 8) is omitted from the introduction. • Methods o Page 8 line 8 “Tinnitus duration > 1 and tinnitus stability > 6 months” – please clarify what the tinnitus duration is required to be for inclusion (> 1 year? > 1 month?) o Why was the cut off for TFI set to greater than 32?

	o Why was Becks Depression Inventory (BDI) score of less than 19 included in the criteria for inclusion? The rationale should be clarified and the the cut off justified. o Failure of “sound therapy” (Page 8 line 19) is included as a therapeutic prerequisite for individuals entering the trial. The introduction indicates that CBT is the only evidence-based treatment for tinnitus burden. Shouldn’t all patients entering the trial, then, have had failure of non-surgical treatment that is supposed by evidence? o Describe any relevant / concomitant care (item 11d) that will be permitted during the study period. For example, if a trial participant wishes to take part in tinnitus retraining therapy, CBT, or masking during the trial, will that be permitted? How will these concomitant interventions be monitored? o Recruitment (item 15) is not adequately described. What assurances can be made that the target sample size can be recruited during that planned study window? For example, how many patients implanted at the study institution would have met inclusion criteria in previous years? o Sample size (item 14): Is the “clinically relevant difference” (page 10, line 9) of 1 grade (15 points) in TFI supported by evidence that indicates this difference is clinically relevant? If so, please cite this evidence. If not, please otherwise justify the selective minimal clinically important difference targeted in the sample size calculation. o Allocation (item 16) requires revision to improve clarity. Please clarify who will generate the allocation sequence and who will assign participants to groups. Please clarify that the block design will be unavailable to those who assign participants until the moment of assignment if this is true. What roles will study investigators or personal who are not blinded to allocation play in the collection or interpretation of data? o Harms (item 22) – indicate what plans are in place for monitoring harms related to the intervention. For example, assessment and documentation of intraoperative or perioperative or post-operative complications, device failures, etc. • Ethics and dissemination o Access to data (item 29) – indicate who will have access to the final trial dataset. • Syntax and grammar errors o Abstract, Page 4 line 16 “promising results were seen to relief tinnitus as a secondary outcome” o Introduction, Page 6 line 16 “burden that patients experience is divers”

REVIEWER	ANGEL RAMOS-MACIAS LAS PALMAS UNIVERSITY . FACULTY OF MEDICINE
REVIEW RETURNED	28-Oct-2020

GENERAL COMMENTS	The authors present a well design protocol. Only some obseevations are proposed to improve this. a) The authors include Bilateral Cases. They must define how they evaluate tinnitus impairment before surgery. b) There is no chapter to Hyperacusis, they of course knows the clinical impact on tinnitus perception of the hypercusis c) It could be important to differentiate those patients in a bimodal condiction (if there is any) and the importance of hearing aid in contralateral ear

	d) As patients are Bilateral deafness, in the inclusion criteria they must indicate how they select the CI side. e) Also would be interest to know which type of CI they are going to use f) And finally they must describe the programming method in these patients

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Peter R Dixon
Institution and Country: University of Toronto
Department of Otolaryngology-Head & Neck Surgery
Toronto, Canada

Comments to the Author
This protocol describes a single centre randomised controlled trial designed to address the question of whether cochlear implantation reduces tinnitus burden for adults with bilateral sensorineural hearing loss whose primary indication for implantation is tinnitus. Novelty is predicated on recruiting patients who would not otherwise have met hearing loss criteria for cochlear implantation in the institution.

The most important flaw of the protocol is justification for the comparator group. Despite evidence to support existing interventions for tinnitus, including cognitive behavioural therapy (Fuller et al. 2020, Cochrane), authors select a comparison group with no intervention. This should be more clearly justified in the protocol. Additional suggestions for improvement are listed below, with associated SPIRIT reporting items listed where relevant.

Additional suggestions:

• Title
The title would benefit from revision to more clearly indicate the population under study. For example, authors might consider some variation of: “Cochlear implantation for tinnitus in adults with bilateral hearing loss: A randomized controlled trial”
Thank you for this valuable remark. We changed the title of our manuscript based on editor’s and reviewers’ advice. The new title is «Cochlear implantation for tinnitus in adults with bilateral hearing loss: protocol of a randomized controlled trial».

• Introduction
The choice of comparator (item 6B) should be more clearly justified. Authors indicate that CBT is supported as a therapy for reducing tinnitus burden but choose a comparator group of no intervention. Why is CBT not compared?
We added the sentence ‘Therefore, we aim to study the effect of cochlear implantation on tinnitus burden in patients suffering primarily from tinnitus and failed standard clinical care. For these patients which also have a accompanied by bilateral moderate to severe hearing loss in a randomized controlled trial will be conducted in which cochlear implantation will be compared to no intervention.’ to the introduction to clarify the choice of a comparator group of no intervention. We think that an invasive therapy as cochlear implantation should only be done in patients which have already tried other treatments. Therefore, one of our inclusion criteria is the failure of regular care including CBT. Therefore, in this study we will compare CI to no treatment.

Description of trial design (item 8) is omitted from the introduction.
• Methods
Page 8 line 8 “Tinnitus duration > 1 and tinnitus stability > 6 months” – please clarify what the tinnitus duration is required to be for inclusion (> 1 year? > 1 month?)
We changed the text accordingly: ‘Tinnitus duration > 1 year and tinnitus stability > 6 months’.

Why was the cut off for TFI set to greater than 32?
Because of the invasive nature of the cochlear implantation, we only want to provide this as a treatment option for patients affected moderately to severely by their tinnitus. The Tinnitus Functional index score results in different tinnitus severity grade. A TFI score greater than 32 corresponds to a tinnitus severity at least moderate. We added a sentence ‘Moderate to catastrophic tinnitus burden: Tinnitus Functional Index >32’ in the inclusion section to clarify the TFI cut off.

Why was Becks Depression Inventory (BDI) score of less than 19 included in the criteria for inclusion? The rationale should be clarified and the the cut off justified.
We learned from the publication of Van de Heyning et al. that a concomittant clinical depression besides severe tinnitus complaints warrants psychiatric therapy instead of indicting an implant (P. Van De Heyning et al., 2007; Paul Van De Heyning et al., 2008). This is the reason for this criterium. The Beck Depression Inventory score results in different depression grade. A BDI score lower than 19 corresponds to no depression to mild depression. We added a sentence ‘No to mild depression: Beck Depression Inventory <19’ in the inclusion section to clarify the BDI cut off.

Failure of “sound therapy” (Page 8 line 19) is included as a therapeutic prerequisite for individuals entering the trial. The introduction indicates that CBT is the only evidence-based treatment for tinnitus burden. Shouldn’t all patients entering the trial, then, have had failure of non-surgical treatment that is supposed by evidence?
We agree with your remark and added one sentence to the introduction: ‘Sound therapy is also considered as a recommendation for patients with hearing loss according to European guidelines’. According to the European Guidelines (Cima et al., 2019), sound therapy, which includes hearing aid, could benefit to patient with hearing loss. Because we are including patients with moderate to moderately severe hearing loss, we included failure of CBT and sound therapy as a prerequisite for inclusion.

Describe any relevant / concomitant care (item 11d) that will be permitted during the study period. For example, if a trial participant wishes to take part in tinnitus retraining therapy, CBT, or masking during the trial, will that be permitted? How will these concomitant interventions be monitored?
No other care will be permitted during the duration of trial. This will be monitored during the trial. Only hearing aids will be allowed as a standard care for their hearing loss in the non-CI ear, for which a sentence is added in the intervention section; ‘Hearing aid will be allowed in the contralateral ear’. Patients will be allowed to use other concomitant interventions after the end of study.

Recruitment (item 15) is not adequately described. What assurances can be made that the target sample size can be recruited during that planned study window? For example, how many patients implanted at the study institution would have met inclusion criteria in previous years?
We are recruiting patient that fall outside the cochlear implant candidacy criteria. Therefore, there is currently no patient implanted at the clinic with the stated criteria. We will recruit patients from our institute though also from outside. This is facilitated by the fact that our center is centrally located in the Netherlands and have shown by previous studies that patients are willing to attend our clinic for such studies from the whole country.

Sample size (item 14): Is the “clinically relevant difference” (page 10, line 9) of 1 grade (15 points) in TFI supported by evidence that indicates this difference is clinically relevant? If so, please cite this

evidence. If not, please otherwise justify the selective minimal clinically important difference targeted in the sample size calculation.
We added the reference to the sample size section. Meikle et al. 2012 defined a minimal reduction of 13 points to be a clinical relevant change. For the study, we consider a change of tinnitus grade severity, which correspond to a reduction of 15 points in the TFI score, to be clinically relevant.

Allocation (item 16) requires revision to improve clarity. Please clarify who will generate the allocation sequence and who will assign participants to groups. Please clarify that the block design will be unavailable to those who assign participants until the moment of assignment if this is true. What roles will study investigators or personal who are not blinded to allocation play in the collection or interpretation of data?
We agree with your suggestion and added the following information in the randomization section: 'A study database was set up in Castor EDC to support allocation and concealment. Investigators enter information for each eligible patient and the randomization assignment is revealed once the investigators validate the inclusion of the patient. The block design is unavailable to those who assign participants until the moment of assignment.'

Harms (item 22) – indicate what plans are in place for monitoring harms related to the intervention. For example, assessment and documentation of intraoperative or perioperative or post-operative complications, device failures, etc.
We added more information about monitoring harms in the adverse events section: 'Besides the normal risks associated with surgery and general anaesthesia, adverse events related to cochlear implantation will be monitored by assessment and documentation of intra- and post-operative complications and device failures. Deterioration of the hearing < 30 dBs (PTA) is expected after implantation because of the cochlear trauma and should not be considered as an adverse event [35,36]. All adverse events will be followed until they have abated or until a stable situation has been reached.'.
• Ethics and dissemination
Access to data (item 29) – indicate who will have access to the final trial dataset.
This information is already in the manuscript (page 15 line 24).
• Syntax and grammar errors
Abstract, Page 4 line 16 "promising results were seen to relief tinnitus as a secondary outcome"

Introduction, Page 6 line 16 "burden that patients experience is divers"

Reviewer: 2
Reviewer Name: ANGEL RAMOS-MACIAS
Institution and Country: LAS PALMAS UNIVERSITY . FACULTY OF MEDICINE

Comments to the Author
The authors present a well design protocol. Only some obseevations are proposed to improve this.

a) The authors include Bilateral Cases. They must define how they evaluate tinnitus impairment before surgery.
Tinnitus burden is evaluated using two questionnaires, the Tinnitus Functional Index (TFI) and a Visual Analogue Scale (VAS). Tinnitus characteristics are assessed using tinnitus matching tests as illustrated in Table 1.

b) There is no chapter to Hyperacusis, they of course knows the clinical impact on tinnitus perception of the hypercusis.
Hyperacussiss is not assessed in this trial. While interesting for future reseach, we focus our study on tinnitus outcomes.

c) It could be important to differentiate those patients in a bimodal condiction (if there is any) and the importance of hearing aid in contralateral ear
We agree and added a sentence in the intervention section: 'Hearing aid will be allowed in the contralateral ear'. Therefore, although of interest, we do not measure specifically the benefit of the hearing aid in the contralateral ear.

d) As patients are Bilateral deafness, in the inclusion criteria they must indicate how they select the CI side.
We agree and added a sentence about the selection of the CI side.

e) Also would be interest to know which type of CI they are going to use
We agree and precised which type of electrode was used for the trial. As described in the intervention section (page 8 line 36), the Nucleus Profile CI622 with a slim straight electrode (or similar) will be used for the trial.

f) And finally they must describe the programming method in these patients
We agree and added a sentence about the programming method in the intervention section: 'The CI fitting will not differ from the standard of care and will be optimized for every patient.'.

VERSION 2 – REVIEW

REVIEWER	Dixon, Peter University of Toronto, Department of Otolaryngology - Head and Neck Surgery
REVIEW RETURNED	29-Mar-2021

GENERAL COMMENTS	Thank you for addressing all previous suggestions.